REMARKS

I. **Status**

All of the claims, Claims 1-15, were rejected in the March 6, 2008 Office Action.

In the above amendments, Applicants have amended Claim 1 to recite that the poorly soluble pharmaceutical compound specifically has a water solubility of less than about 1 mg/ml. Support for such amendment can be found in the subject application as originally filed, for example at page 2, lines 31-33.

Applicants further amend Claim 1 to further specify the nature of the functional polymer. Specifically, Claim 1 is amended to recite that the functional polymer is acidic. Support for such amendment can be found in the originally filed patent application, for example at page 3, lines 33-36, wherein the specification states that, in one aspect, especially preferred for the conjugation of insoluble drugs that are basic, e.g. ziprasidone and the like, the functional polymers are preferably acidic.

Furthermore in Claim 1, amendments are herein made to specify that the acidic functional polymer is selected from carboxyl bearing coplyester carbonates and carboxyl-bearing polyesters made by ring-opening polymerization of a list os specific cyclcic monomers or that the acidic functional polymer is a carboxyl-bearing polypeptide. Support for such amendment to Claim 1 can be found in the originally filed specification.

For example, on page 3, line 36, through page 4, line 5, the originally filed specification states that an acidic functional polymer for use with a basic drug can be a carboxyl-bearing polyester or a carboxyl-bearing copolyester carbonate made by ring-opening polymerization of one or more cyclic monomers lactide (L), glycolide (G), p-dioxanone (PD), ε-caprolactone (CL), 1,5-dioxepan-2-one (DOP), and trimethylene

carbonate (TMC), meaning that said polyester or copolyester can be made from a single such monomer or a mixture of such monomers, and this is described in the specification.

On page 4, lines 20-22, the originally filed application states that in another aspect, carboxyl-bearing polpeptides can be employed as the functional polymer to form ionic conjugates with a drug, preferably a basic drug.

Claim 2 is canceled, without prejudice, in the above amendments. It is believed that the elements of Claim 2 are incorporated into Claim 1 in the above amendments.

Claim 3 is amended in the above amendments to clarify that in one embodiment, an embodiment wherein the functional polymer comprises a cycldextrin, the functional polymer is a carboxyl-bearing cyclodextrin water insoluble derivative. Support for such amendment is found in the originally filed application, for example at page 4, line 26, wherein it is stated that the functional polymer, in another aspect, *comprises* a sachharide (emphasis added herein). On page 5, lines 4-15, of the originally filed application, this aspect is described as being in one example an insoluble cyclodextrin derivative made by mixed partial acylation of cyclodextrin with a fatty acid anhydride and a cyclic anhydride followed by grafting the unacylated hydroxylic group of said cyclodextrin with one or more of certain cyclic monomers.

Claim 3 is also amended to correct some spelling errors in the recited cyclic monomers.

Claims 8, 10 and 15 are likewise amended to correct the same spelling errors in certain of the recited cyclic monomers.

Claims 9 and 10 are amended to correct an improper dependency. As amended, Claims 9 and 10 are now dependent from Claim 6 instead of Claim 4.

In the above amendments, Applicants add new Claims 16 and 17 to clarify and claim the subgenera wherein the functional polymer comprises a cyclodextrin or a cyclic oligosaccharide derivative with carboxyl groups on the outer surface. Support for these Claims can be found in the originally filed specification, for example at page 4, lines 26-27, wherein the specification states "in another aspect, the functional polymer comprises a saccharide, including without limitation a cyclic oligosaccharide derivative with carboxyl groups on the outer surface", and on page 4, lines 28-29, wherein the specification states "examples of such a saccharide are cyclodextrins, especially those that have been functionalized to incorporate one or more carboxyl groups."

As support for all of the above amendments can be found in the originally-filed application, Applicants contend that these amendments do not raise any issue of new matter and respectfully request that these amendments be entered.

Upon entry of the amendments herein, Claims 1, 3-11, and 13-17 will be pending in the application. Reconsideration is respectfully requested in light of these amendments and the following remarks.

II. Amended Claims 1, 4-7, 9 and 11-14 Satisfy the Written Requirement and Do not Introduce New Matter

The Examiner rejected claims 1, 4-7, 9 and 11-14 under 35 U.S.C. § 112, as allegedly failing to comply with the written description requirement. According to the Examiner, the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner stated that this was a new matter rejection. The Examiner objected to the term

"carboxyl bearing copolyester" which was added by the amendment to claim 1 in the communication submitted by Applicants on January 28, 2008.

Without agreeing to the Examiner's allegations about the phrase "carboxyl-bearing copolyesters", Applicants believe that the amendments herein render moot the Examiner's objection.

III. The Amended Claims Are not Obvious Over Kim et al. and Patent '883

The Examiner rejected claims 1-8 and 10-15 under 35 U.S.C. § 103(a) as allegedly being unpatentable over US 6,232,304 to Kim et al. (hereinafter "Kim et al.") in view of US 5,916,883 to Shalaby et al (hereinafter "Patent '883"). (The Examiner referred to Shalaby et al. as "US 5,916,833"; however, Applicants assume the Examiner meant "US 5,916,883"). The Examiner argues that some of the cyclodextrin derivatives disclosed by Shalaby et al. in Patent '883, such as the "ACDs" ("acylated cyclodextrin") mentioned in Table II, Examples 1 and 2, are functional polymers for some embodiments of the present invention. The Examiner argues that it would have been *prima facie* obvious to a person of ordinary skill in the art, at the time of the invention, to use the ACDs of Shalaby et al. instead of the "regular" cyclodextrins of Kim et al. in the subject application.

Applicants respectfully traverse the above-described rejection. It is true that a carboxyl-bearing cyclodextrin water insoluble derivative taught by Patent '883 can be ionically conjugated with a low solubility drug to form a solid ionic conjugate as claimed in the subject application, and Applicants so state in the subject application, for example at Page 5, lines 7-15 of the subject application. However, Patent '883 does not at all

indicate such utility. The teaching of Patent '883 is limited to highly soluble drugs and, accordingly, there is no reason for a person of ordinary skill in the art to use any of the polymers described in Patent '883 with a highly insoluble compound, like ziprasidone.

Shalaby et al. in Patent '883 teach carboxyacylated cyclodextrins. These cyclodextrin derivatives are used to form ionic sustained release compositions to allow for a controlled release of highly soluble drug in the body. (See Col. 1, lines 16-20 of Shalaby et al.). Shalaby et al. in Patent '883 used cyclodextrin derivatives wherein at least 60 percent of the free hydroxy groups of the cyclodextrin were acylated with acyl groups where at least one of the acyl groups comprised a free carboxylic group (see Col. 1, lines 23-27 of Shalaby et al.). The focus in Patent '883 is on cyclodextrin derivatives; cyclodextrin is an essential element of the invention described therein. Moreover, the cyclodextrin in Patent '883 is derivatized in a special way to effect a controlled release of polypeptide drugs which are of high solubility.

In Kim et al., the focus is also on cyclodextrins. But Kim et al. teaches generally the use of cyclodextrins to increase the solubility of a low solubility drug, ziprasidone. One of ordinary skill in the art would not be inclined to derivatize a cyclodextrin in the way taught by Patent '883 for use with ziprasidone, ziprasidone being a low solubility drug. Why would a person of ordinary skill modify cyclodextrin in such an extravagant manner as taught by Patent '883 to increase ziprasidone solubility when Kim et al. already provides simpler, specific examples of cyclodextrins to achieve ziprasidone solubilization? For example, Example 1 of Kim et al. uses the cyclodextrin SBECD to solubilize ziprasidone. The structure of SBECD can be seen in Figure 1 of the attached reference Gage et al. (Journal of Pharmaceutical and Biomedical Analysis, 22 (2000)

773-780). SBECD, as seen from Figure 1 of Gage et al., comprises just seven sugar molecules. In contrast, the examples in Patent '883 involve first acylating a β-cyclodextrin[1] (see Example 1 of Patent '883 and note the relatively heavy weights shown in Table I for such acylated cylodextrin), and then forming a conjugate with a water soluble polypeptide drug (see Example 3 of Patent '883). The thus-modified cyclodextrin were shown in Patent '883 to be efficacious for use with *high* solubility drugs, not with *low* solubility drugs.

As recited in the claims of the instant application, a functional polymer is used in combination with a low solubility drug, and Applicants have amended the Claims of the subject application to specify a particular maximum solubility of the drug in order to further highlight this difference. Moreover, unlike Patent '883 or the Kim et al. Patent, cyclodextrin is not an essential element of the subject invention as recited in the Claims. Only in one aspect does the subject invention use functional polymer comprising cyclodextrin. In other words, a functional polymer comprising a cyclodextrin is just one embodiment or subgenera of functional polymer that can be used to form the solid ionic conjugates of the subject invention as recited in the Claims. Applicants have added new Claims 16 and 17, directed to the subgenera wherein the functional polymer of the claimed solid ionic conjugate comprises a cyclodextrin or a cyclic oligosaccharide derivative to clarify this point. It is true that a species can anticipate a genus; however, the instant situation is not a case of anticipation: Patent '883 does not disclose a low solubility drug, and Kim et al. does not disclose a polymer. Thus, neither reference anticipates any Claim in the subject application. Nor does the combination render

[1] Applicants note that SBECD is also a β-cyclodextrin.

obvious the invention as recited in the subject Claims for the reasons explained fully herein.

The Examiner also argues that obviousness stems from the statement in Patent '883 that ACDs are useful with drugs containing an ionizable amine. The Examiner correctly points out that ziprasidone has two ionizable amines. However, the statement in Patent '883 must be looked at in context. The focus of Patent '883 is providing a method for affecting a controlled release of *highly* soluble drugs. In this context, Patent '883 can be understood to be saying that ACDs work well with highly soluble drugs that have an ionizable amine. While ziprasidone has two ionizable amines it is known to be a very insoluble drug.

The solubility of ziprasidone free base and several pharmaceutically acceptable salts of ziprasidone are provided in WO 2005/020929, herewith. As can be seen on page 7 of WO 2005/020929, of the listed compounds in Table 1, only ziprasidone fumarate has an aqueous solubility of greater than 1 mg/ml. Kim et al. (Journal of Pharmaceutical Sciences, Vol 87, No. 12, 1560-1567 (December 1998)) provides the aqueous solubility of additional ziprasidone salts, which also have aqueous solubility of less than 1 mg/ml (see Table 1 on page 1561 of Kim et al.).

The above two references are listed on the Information Disclosure Citation form submitted herewith, and the Examiner is kindly requested to initial the form beside each listed reference where indicated after his review.

In contrast, the solubility of the peptides, Lanreotide™ and Decapeptyl™, that Shalaby et al. worked with in Patent '883 is much higher. This can be seen from Example 3 in Column 4 of Patent '883. The Patent states that "a concentrated, cold

solution *(3-15 weight/volume percent)* of the acetate salts of the polypeptides Lanreotide™ ....or Decapeptyl™ was added ...." (emphasis added). Thus, a concentrated solution of these drugs contained 30-150mg/ml water, an amount of dissolved drug that is at least about 30-150 times greater than the amount of ziprasidone or ziprasidone salt dissolvable in water.

The Examiner further asserts that the fact that ziprasidone had previously been used with cyclodextrins to great effect in Kim et al. would have made it a particularly appealing drug to use with the ACDs in Patent '883, and also goes toward the expectation of success. However, Patent '883 only used derivatized cyclodextrins with high solubility drugs, and further Patent '883 used cyclodextrins derivatized in a specific manner to make them useful for controlled release of the high solubility drugs. One of ordinary skill in the art would not use a compound the purpose of which was to function with highly soluble drugs with low solubility drugs. In fact, a disincentive to use specially-derivatized cyclodextrin as described in Shalaby et al. with low solubility drugs clearly existed. One skilled in the art, who was trying to find a method of increasing the solubility of low solubility drugs, would be reluctant to use the very compound which had been shown to be effective for high solubility drugs. The prior art clearly taught away from this invention. In *United States v. Adams*, 383 US 39, 51-52 (1966) the Court held that even an invention which only substitutes one known element for another is not considered obvious if the prior art teaches away from combining the two elements. Here, the reference, Shalaby et al., teaching that carboxyacylated cyclodextrin is effective for use with high solubility drugs taught away from trying to use these same compounds with low solubility drugs.

The Examiner also contends that the claimed invention is no more than picking art-known materials and combining them to obtain predictable and art-expected results. However, showing that each element was independently known in the art is not enough. *See KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727, 1741 (2007). Although *KSR* warned against a rigid application of the TSM (teaching, suggestion, or motivation) test, some reason for combining the two elements must still exist:

> [A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the art. . . [I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant art to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in come sense, is already known. *Id.* at 1741.

Here, there is not only no motivation to combine these two prior arts but a disincentive actually exists as discussed above. One skilled in the art would not be motivated to use a compound which had been shown to be effective with highly soluble drugs for use with highly insoluble drugs.

KSR also explained that when there are a "finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *Id* at 1742. Here, the issue at hand is a method for increasing the solubility of basic drugs. Given the teachings of Kim et al. regarding use of cyclodextrins to solubilize a low solubility drug like ziprasidone, it would have been highly unusual for a person of ordinary skill in the art to go outside the scope of the specific examples of Kim et al. and explore the infinite areas of solubilization technology to solubilize ziprasidone. The combination of a carboxyl bearing copolyester and a basic

drug was therefore not "obvious to try". *Id.* Claims 1-8 and 10-15 should therefore not be considered obvious in violation of 35 U.S.C § 103(a).

IV. Amended Claim 9 is not Obvious over Kim et al. and Shalaby

The Examiner rejected claim 9 under 35 U.S.C. § 103(a) as being unpatentable over the Kim et al. Patent in view of Patent '883 as applied to claims 1-8 and 10-15, and further in view of US 3,418,329 to Roberts et al. However this rejection is moot in light of the arguments above. Roberts et al. does not contribute anything new to this field other than teaching vegetable oil as a carrier for drug compositions. The teaching of Roberts et al. relates to the prevention of peptic ulcers, not solubility.

Based on the amendments to the Claims herein and the arguments presented above, Applicants request reconsideration and withdrawal of this rejection.

V. Conclusion

Having addressed all outstanding issues, Applicants kindly request removal of all rejections and allowance of the Claims as amended herein. To the extent the Examiner believes it would facilitate allowance of this case, the Examiner is urged to call the undersigned at the number below.

No other fee besides the fee for the Three Month Extension of Time authorized with this submission is believed necessary for this submission. However, to the extent any additional fee is due, the Commissioner is hereby authorized by this paper to charge any required fees or credit any overpayment to Deposit Account 16-1445.

Respectfully submitted,

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